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[54] **ADJUVANTS FOR RECTAL DELIVERY OF DRUG SUBSTANCES**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 213,121, Dec. 5, 1980, abandoned, which is a continuation-in-part of Ser. No. 105,645, Dec. 20, 1979, abandoned.

[51] **Int. Cl.**[3] **A61K 31/43;** A61K 31/54; A61K 31/425; A61K 31/625

[52] **U.S. Cl.** **424/232;** 424/230; 424/246; 424/270

[58] **Field of Search** 424/230–235, 424/365, 270, 248, 271

[56] **References Cited**

PUBLICATIONS

Chemical Abstracts, 83, 205953y (1975) Toyoshima et al., Insulin Complex Salts with Aminobenzoate Derivatives.

Chemical Abstracts, 71, 89823g (1969) Sugimoto, Isao, Complexes XVI-Effect of Complex Formation on Drug Absorption etc.

Pharmaceutical Res. Laboratory, Yakugaku Zasshi, 88(5)618–622, Studies on Complexes–Effect of Complex Formation on Drug Absorp. etc.

CA 69–65889 (17)–Complexes–Effect of Complex Formation on Drug Absorption from Alimentary Tract, Susimoto, Isao et al., Tanabe Seiyaku Co. Ltd., Osaka, Yakusaku Zasshi V88F(6) pp. 690–694 (1968).

CA 69–50670 (13), Complexes, Effect of Complex Formation Drug Absorption from Alimentary Tract, Susimoto, Issao, Tababe Seiyaku Co., Ltd., Japan Pharm. Bull. 16(6), pp. 1098–1104 (1968).

CA 69-94857(23) Complexes, Effect of Complex Formation on Drug Absorption from Alimentary Tract, Susimoto, Isao, Tanabe Seiyaku Co., Ltd., Pharm. Res. Chem. Bull. 16(8) pp. 1527–1532 (1968).

CA 71–33382(8) Complexes, Effect of Complex Formation on Drug Absorption from Alimentary Tract, Susimoto, Isao Tanabe Seiyaku Co. Ltd., Pharm. Res. Chem. Pharm. Bull. 17(5) pp. 994–998 (1969).

Shunji Ota Dept. Pharmacol. Showa Med. Col. Comments: Jap. 5 Pharm. 51 pp. 692–714 (1955) Influence of Various Substances on the Absorption of Histamine from the Large Intestine etc.

Microbiologic Pharmacologic Properties of New Ampicillin Deriv. etc. by Valcavi, R. Caponi et al.

Journal of Pharmaceutical Sciences, vol. 57, No. 8 (1968) Reuning et al., Effect of Complex Formation on Drug Absorption etc., pp. 1335–1341.

Journal American Pharm. Assoc. No. 9, pp. 527–530, Investigation of Complex Formed in Solution by Caffeine, Higuchi et al.

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[57] **ABSTRACT**

A method and drug form for enhancing the rate of absorption of a rectally administered drug from the rectal compartment into the blood stream of a warm blooded animal. The method includes the steps of preparing a β-lactam drug form capable of being rectally administered. The drug form comprises a therapeutically effective unit dosage amount of a selected drug of the type which is capable of being absorbed into the blood stream from the rectal compartment and hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof, the hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof being present in the drug form in a sufficient amount to be effective in enhancing the drug absorption rate, when rectally administering the drug form to warm blooded animals.

19 Claims, No Drawings

ADJUVANTS FOR RECTAL DELIVERY OF DRUG SUBSTANCES

REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part application of our co-pending application Ser. No. 213,121, filed Dec. 5, 1980, abandoned, which is a continuation-in-part application of Ser. No. 105,645 filed Dec. 20, 1979, and now abandoned.

BACKGROUND OF THE INVENTION

Field of the Invention and Description of the Prior Art

This invention relates to a method for administering drugs to warm blooded animals by rectal delivery and it particularly relates to a method for enhancing the rate of absorption of such rectally delivered drugs from the rectal compartment to the blood stream; this invention also relates to improved rectal suppository drug forms used in the practice of such method.

One known method of drug administration is accomplished by the incorporation of a drug in a "suppository", which generally speaking, is a medicated solid dosage form generally intended for use in the rectum, vagina, and to a lesser extent, in the urethra. Molded rectal suppositories usually employ vehicles that melt or soften at body temperatures so that the drug may be released for use. On the other hand, soft elastic gelatin capsule suppositories rely on the presence of moisture in the rectum which causes the capsule to open and release its liquid contents which contains its therapeutic agent. Drugs administered in suppository form are administered for either local or systemic effect. The action of the drug is dependent on the nature of the drug, its concentration, and its rate of absorption. Although rectal suppositories are commonly used for the treatment of constipation and hemorrhoids, that is, for local effect, such rectal suppositories are also administered rectally for systemic action. A wide variety of drugs may be rectally administered, as by the use of suppositories, including, for example, analgesics, antispasmodics, sedatives, tranquilizers, and antibacterial agents.

Rectal drug administration has many advantages over other routes of drug administration, such as oral administration and parenteral administration. For example, many drug substances that are given orally undergo inactivation in the stomach because of the acidic, enzymatic content of the stomach or the drug may be subject to digestive attack in the gut and/or to microbial degradation in the lower gut. Oral administration of drugs also directs all of the absorbed substances through the liver where they can be inactivated or reduced in effectiveness.

Rectal administration overcomes wholly, or in part, these known disadvantages of oral drug administration. Rectal drug administration also has advantages over parenteral administration. For example, rectal drug administration does not require highly trained personnel required for parenteral administration and also represents significantly less hazard to te patient.

In view of the known disadvantages or oral and parenteral drug administration, drug administration by rectal delivery enables many drugs to be absorbed from the anorectal area, and yet retain their therapeutic value. The lower hemorrhoidal vein, surrounding the colon and rectum, enters the inferior vena cava and thereby bypasses the liver. Therefore, drugs are absorbed directly into the general circulation when rectally administered. For further background on rectal delivery of drugs, reference is made herein to an article entitled "Rectal Administration of Drugs" by N. Senior, "Advances in Pharmaceutical Sciences", edited by Bean, Beckett, and Corlass, Volume IV, Academic Press (1974) and to Chapter 8, "Suppositories", by Joachim Anschel and Herbert A. Lieberman, Lachman and Lieberman "Theory and Practice of Industrial Pharmacy", Lea and Febiger (1976).

Despite the known advantages of rectal administration of drugs, the rectal administration of drugs is not totally without problems. First, many rectally administered drugs are poorly absorbed while others are slowly absorbed and, if so, are often inactivated or degraded while still in the rectal compartment. It would therefore be highly advantageous if rectally administered drug substances could have their rate of absorption from the rectal compartment to the blood stream enhanced.

SUMMARY OF THE INVENTION

It is therefore an important object of the present invention to provide a unique method for enhancing the absorption rate of rectally administered drugs from the rectal compartment to the blood stream.

It is also an object of the present invention to provide an improved rectal suppository drug form which enhances the absorption rate of rectally delivered drugs contained in a soft elastic gelatin capsule or a molded suppository.

It is a further important object of the present invention to provide an improved method for administering drugs by the use of rectal suppositories wherein enhanced absorption results from the incorporation of hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof into the drug formulation.

It is yet another important object of this invention to provide an improved rectal suppository having an enhanced absorption rate of a selected drug therefrom when in the rectal compartment, wherein hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof are incorporated into a drug formulation contained within a soft elastic gelatin capsule or molded type of rectal suppository.

Further purposes and objects of this invention will appear as the specification proceeds.

The foregoing objects are accomplished by providing a method and suppository drug form wherein the absorption rate of rectally administered drugs into the bloodstream of warm blooded animals is enhanced, the method comprising the steps of preparing a drug form capable of being rectally administered, the drug form comprising an effective unit dosage amount of a drug of a type which is capable of being absorbed from the rectal compartment into the blood stream and hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof, the hydroxy aryl or hyroxy aralkyl acids or salts, amides or esters thereof being present in said drug form in an amount sufficient to be effective in enhancing the absorption rate of a drug into the blood stream from the rectal compartment, and thereafter rectally administering the drug form to a warm blooded animal.

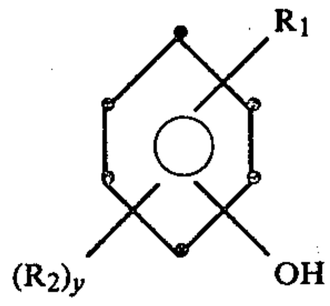
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention, generally, comprises the steps of preparing a drug form capable of being rectally administered, wherein the drug form comprises an effec-

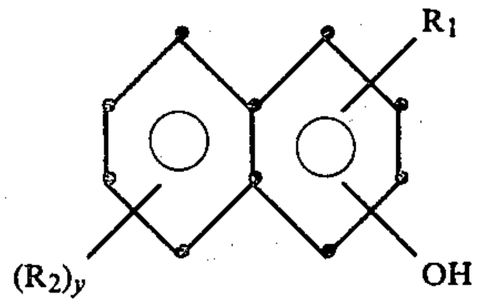
tive unit dosage amount of a drug capable of being absorbed into the blood stream of a warm blooded animal from the rectal compartment and hyroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof, the hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof being present in the drug form in a sufficient amount to be effective in enhancing the absorption rate, and rectally administering the drug form to the warm blooded animal.

Our method for enhancing the rate of absorption of drugs from the rectal compartment is useful for a wide range of drugs or drug categories including, β-lactam antibiotics such as penicillin, including penicillin G., penicillin V., ampicillin, amoxicillin, methacillin, carbenicillin, ticaricillin and cephalosporins, such as cephalosporin C, cefazolin, cefoxitin, cephamandole, cefuroxine, cephaprin, cephaloridine, cephmetazole, cepheperin, cephanone, oxacephalosporin, S-6059, and T-1551 all of which drugs are capable of being absorbed into the blood stream of a patient from the rectal compartment. Other specific drugs useful in the method and in combination with the hereinafter described adjuvants will be hereinafter identified. The amount of the drug used in our method for enhancing drug absorption varies over a wide range, generally any therapeutically effective unit dosage amount of the selected drug is used.

The hydroxy aryl or hydroxy aralkyl acids or salts, amides or esters thereof, that are used as the adjuvants in our method and in our suppositories, have the following structural formulae including the various isomers possible within the formulae set forth:

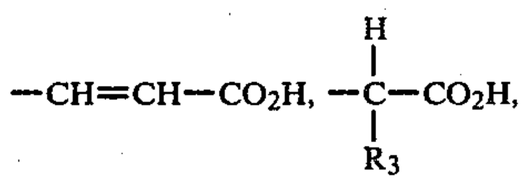


I.



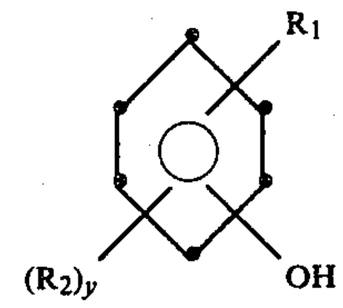
II

wherein R_1 is a radical selected from $-CO_2H$, $-(CH_2)_n-COOH$,

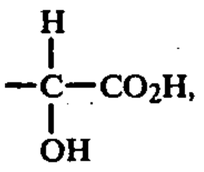


$-SO_3H$, $-CH_2SO_3H$, $X(CH_2)_nCO_2H$, SO_2NHR_4, $PO(OH)N(OH)_2$, $PO(OH)OR_4$, or a pharmaceutically acceptable salt thereof
wherein R_2 is a radical selected from OH, H a lower alkoxy radical having 1–10 carbon atoms, a lower alkyl radical having 1–10 carbon atoms, a lower alkenyl radical having 2–5 carbon atoms, a lower alkanoyl radical having 1–5 carbon atoms, a carboxy radical, a carbo-lower alkoxy radical having 1–5 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical having 1–5 carbon atoms, an amino radical, a mono- or di-lower alkyl amino radical having 1–5 carbon atoms, a carbamyl radical, a lower mono- or di-alkyl carbamyl radical wherein the alkyl group has 1–5 carbon atoms, a thio radical, a lower alkyl thio radical wherein the alkyl group has 1–5 carbon atoms, a cyano radical, a lower alkyl sulfone radical wherein the alkyl group has 1–5 carbon atoms, a lower alkyl sulfoxide radical wherein the alkyl group has 1–5 carbon atoms, a nitro radical, $N(CN_2)_2$, $C(CN)_3$, an alkynyl radical having 2–6 carbon atoms, a cycloalkyl radical having 3–10 carbon atoms, a cycloalkenyl radical having 3–10 carbon atoms, an aryl radical including phenyl, a hetroaryl radical including thiophenyl and imadazoalyl, or a heterocycloalkyl radical including morphilinyl and piperdinyl,
wherein R_3 is a straight or branched alkyl radical having 1–6 carbon atoms or a hdroxy radical,
wherein R_4 is H or a lower alkyl radical having 1–5 carbon atoms,
wherein X is O or S,
wherein n is an integer of 0–5,
wherein y is 1 or 2, and
when y is 2, both the R_2 radicals, taken together, can form a ring containing O, N or S.

More preferred adjuvants are those having the formula:

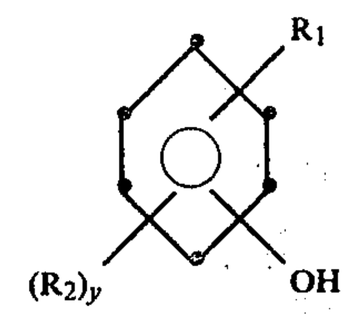


wherein R_1 is a radical selected from $-CO_2H$, $-(CH_2)-COOH$, $-CH=CH-CO_2H$,

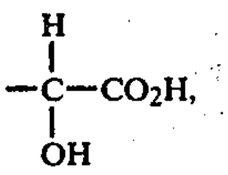


$-SO_3H$, $-CH_2SO_3H$, or $O(CH_2)\ CO_2H$
or a pharmaceutically acceptable salt thereof wherein R_2 is selected from OH, H, a lower alkoxy radical having 1–10 carbon atoms, a lower alkyl radical hving 1–10 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical wherein the alkyl group has 1–5 carbon atoms, a lower alkyl thio radical wherein the alkyl radical has 1–5 carbon atoms, a cycloalkyl radical having 3–10 carbon atoms, or a cycloalkenyl radical having 3–10 carbon atoms and wherein y is an integer of 1 or 2.

Highly preferred adjuvants are those having the formula:



wherein R1 is CO_2H, $-(CH_2)-COOH$,



or SO_3H, or a pharmaceutically acceptable salt thereof wherein R_2 is OH, H, a lower alkoxy radical, including methoxy, ethoxy, butoxy, or octyloxy, a lower alkyl

radical including methyl, isopropyl, ethyl, t-butyl, n-butyl, or t-octyl, a halo radical, or a tri-halo lower alkyl radical including trifluoromethyl, and wherein y is an integer of 1 or 2.

Specific adjuvants useful in our method and drug forms include salicyclic acid; 5-methoxy salicylic acid; 3,4-dihydroxyphenylacetic acid, (DOPAC); and homovanillic acid; as well as the sodium salts thereof.

As in the case of the drugs used in our method and suppositories, the amount of adjuvant used may vary over a wide range; in general, the identity and the amount of the adjuvant used in connection with the drug are selected in order to be effective in enhancing the absorption rate of the drug from the rectal compartment into the bloodstream.

Generally the amount of adjuvant in our drug forms (suppositories) is from 100–1000 mg in each unit dose. The percentage of adjuvant in the total combination of drug plus adjuvant is 20–95% with a preferred ratio of adjuvant in the total combination of adjuvant plus drug being 30–60%. A most preferred ratio of adjuvant to adjuvant plus drug is 50%.

The particular method used for the rectal administration of the drug and the adjuvant is preferably by use of the appropriate size, shape or form of any of the various types of rectal suppositories known to the pharmaceutical art; alternatively, the drug may be administered with the adjuvant by means of microenema. Useful rectal suppositories with which the present method may be used include cocoa butter suppositories, synthetic fat suppositories, and gelatin capsules including soft elastic gelatin capsule type suppositories as well as other controlled release devices such as an osmotic pump or other polymeric devices.

A preferred form of suppository comprises a soft elastic gelatin capsule having an outer shell which encloses the drug and the adjuvant in a suitable vehicle which will not attack the walls of the seamless gelatin capsule. The shell encapsulates a preselected drug form and the adjuvant. The gelatin capsule shell may be formulated in accordance with conventional techniques for making filled, seamless, soft elastic gelatin capsules containing therapeutically effective unit dosage amounts of the active drug ingredient. For example, one conventional shell formulation includes about 30–53 parts by weight of gelatin, 15–48 parts by weight of a plasticizer, such as glycerine or sorbitol, and about 16–40 parts by weight of water. Additionally, the gelatin shell may contain preservatives such as mixed parabens, ordinarily methyl or propyl parabens in about a 4:1 ratio. The parabens may be incorporated in the shell formulation in minor proportions as compared to the total weight of the shell formulation. Conventional gelatin capsules utilize gelatin having a bloom value of about 160–200 although this amount may be varied.

In a conventional manner, the gelatin composition is mixed and melted under vacuum conditions. The capsules may be simultaneously formed and filled using a conventional method and apparatus such as disclosed, for example, in U.S. Pat. Nos. 1,970,396; 2,288,327; and 2,318,718. The gelatin capsules are formed into a desired shape and size for insertion into the rectal compartment. It is to be understood, however, that the particular method used for making the soft elastic gelatin shell and for incorporating the fill therein are not considered part of the invention herein.

One of the more important uses of our method and suppository for rectal administration of drugs is in the administration of sustained release or programmed release drug forms which will slowly release the drug substances into the rectal compartment of a warm blooded animal. The present method and suppository permit the rapid clearance of the released drug into the blood stream by way of the lower hemorrhoidal vein, instead of moving upwards into the lower gut. This technique thereby reduces or avoids loss of drug effectiveness associated with passage of the drug through the liver.

The following data sets forth specific experiments illustrating various embodiments of the present invention.

EXAMPLE I

The effect of the salicylate type absorption adjuvants on the rectal absorption of β-lactam antibiotics in the Beagle dog is presented in the accompanying tables. The dog model is as previously described except that the blood samples are assayed for antibiotic activity and/or drug concentration using a microbiological assay and/or a high pressure liquid chromatographic technique. As a relative measure of rectal drug delivery, data are presented as "bioavailability" where 1.00 is equivalent to i.v. administration of the target drug.

Referring to Table I, the effect of sodium 5-methoxysalicylate, sodium salicylate, and sodium homovanillate on the rectal absorption of cefmetazole is shown. Clearly, these adjuvant compounds dramatically enhance the rectal absorption of cefmetazole compared to those formulations which contain no absorption adjuvant.

Referring to Table II, the effect of sodium 5-methoxysalicylate on the rectal absorption of cefoxitin is presented. In this instance the best formulation containing absorption adjuvant increased rectal bioavilability 13-fold.

Referring to Table III the effect of sodium 5-methoxysalicylate on the rectal absorption of Penicillin G is demonstrated. In this instance, the best formulation with adjuvant afforded total delivery of the drug, compared to a delivery of 4% for the same formulation without absorption adjuvant.

TABLE I

Relative bioavailability* of sodium cefmetazole after rectal administration compared with intravenous administration with various absorption adjuvants (Beagle dog model).

	Dose of Adjuvant (mg/body)	Sodium 5-methoxy-salicylate	sodium salicylate	sodium homovanillate	
Rx I	(150 mg of sodium cefmetazole) + (adjuvant) + (Witepsol H-15) = 1 g				
	200	—	0.90 ± 0.13	0.90 ± 0.11	(n = 2)
	150	0.94 ± 0.20	0.82 ± 0.20	0.73 ± 0.15	(n = 4)
	100	0.92 ± 0.16	0.56 ± 0.21	0.59 ± 0.24	(n = 2)
	75	0.30 ± 0.05	0.34 ± 0.10	0.35 ± 0.09	(n = 4)
	0	0.05	0.05	0.05	(n = 3)

TABLE I-continued

	Relative bioavailability* of sodium cefmetazole after rectal administration compared with intravenous administration with various absorption adjuvants (Beagle dog model).			
	Dose of Adjuvant (mg/body)	Sodium 5-methoxy-salicylate	sodium salicylate	sodium homovanillate
Rx II	(150 mg of the free acid of cefmetazole) + (adjuvant) + (Witepsol H-15) = 1 g			
	150	0.69 ± 0.21	0.69 ± 0.25	0.50 ± 0.21 (n = 4)
	100	0.63 ± 0.26	0.44 ± 0.20	0.40 ± 0.12 (n = 2)
	0	0.05	0.05	0.05 (n = 2)
Rx III	(150 mg of sodium cefmetazole) + (adjuvant) + (phosphate buffer) = 1 mL			
	300	0.37 ± 0.09	0.30 ± 0.07	— (n = 4)
	150	0.18 ± 0.04	0.14 ± 0.04	— (n = 4)
	0	0.02	0.02	

*Bioavailability = $\frac{[AUC_{rectal}] \times \text{dose i.v.}}{[AUCi.v.] \times \text{dose rectal}}$

BA ± SD

TABLE II

	Rectal Bioavailability of Cefoxitin					
Dosage form and base	Dose of Cefoxitin mg/body	Dose of 5-methoxy salicylate mg/body	[AUC]* mg min/mL	Rectal Bioavailability with adjuvant relative to without $[AUG]_p(dose)_a$ $[AUC]_a(dose)_p$	Rectal Bioavailability relative to IV $[AUC]_r(dose)_{iv}$ $[AUC]_{iv}(dose)_r$	n
i.v.-injection	50	—	1074 ± 111			4
rectal administration-						
suppository-	150	—	82 ± 30		0.05	4
Witepsol H-15	75	50	587 ± 233**	14	0.36	4
	75	75	828 ± 231**	20	0.51	4
	75	100	1050 ± 250**	26	0.65	4
microenema-	75	100	481 ± 123**	12	0.30	4
gelatin gel	75	200	1242 + 192**	30	0.77	4
buffer solution	75	150	189 ± 52**	5	0.12	4

*$[AUC] = [AUC]_{0\ min.}^{120\ min.}$

**p 0.001 versus rectal administration in absence of adjuvant.

Subscripts:
$_r$ = rectal administration,
$_{iv}$ = IV administration,
$_p$ = adjuvant present,
$_a$ = adjuvant absent

TABLE III

	Rectal Bioavailability of Penicillin G					
Dosage form and base	Dose of Penicillin G mg/body	Dose of 5-methoxy salicylate mg/body	[AUC]* mg min/mL	Rectal Bioavailability with adjuvant relative to without $[AUC]_p(dose)_a$ $[AUC]_a(dose)_p$	Rectal Bioavailability relative to IV $[AUC]_r(dose)_{iv}$ $[AUC]_{iv}(dose)_r$	n
i.v.-injection	50	—	288 ± 46			4
rectal administration-						
suppository-	150	—	38 ± 3		0.04	4
Witepsol H-15	75	50	178 ± 19**	9	0.41	4
	75	75	249 ± 64**	13	0.58	4
	75	100	450 ± 208**	24	1.04	8
microenema-	75	100	160 ± 56**	8	0.37	8
gelatin gel	75	150	301 ± 73**	16	0.70	4
buffer solution	75	150	149 ± 29**	8	0.35	4

*$[AUC] = [AUC]_{0\ min.}^{120\ min.}$

**p 0.001 versus rectal administration in absence of adjuvant, t-test.

Subscripts:
$_r$ = rectal administration,
$_{iv}$ = IV administration,
$_p$ = adjuvant present,
$_a$ = adjuvant absent

EXAMPLE II

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of significant drugs which are rectally administered, from the rectal compartment into the blood stream, is demonstrated with an in situ perfusion method of the rectum. The rectum of a male Sprague-Dowley rat weighing 275–300 g., is exposed by an abdominal incision, a glass cannula is inserted into the distal direction and tied firmly to keep it in position. A second cannula is in-

serted through the anus 1 cm. inside the rectum and secured by ligation. Thus, about 2 cm. of the rectum is exposed to the perfusate. The perfustate (6 ml.) is circulated at a rate of 2 ml./min. at 38° C. As perfustate, 1/15 M-phosphate buffer solutions are used and the ionic strength of the perfusate is adjusted to 0.75 with sodiumchloride as necessary. The adjuvant is employed at a concentration of 0.5%, while the concentration of the various drugs is varied in accordance with the known effective dosages for said drugs. The amount of drug remaining in the perfustate is analyzed as a function of time by appropriate methods, e.g., by high-pressure liquid chromatography. Blood levels are also measured in blood samples taken from a vein in the leg of the rat. The results of this method show that the percent absorption of the various drugs after 1 hour from the perfusate in the rat rectum is significantlty enhanced by the presence of an adjuvant of the present invention.

Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

	Drug	Adjuvant
1.	Ampicillin	sodium salicylate
2.	Amoxicillin	sodium homovanillate
3.	Methacillin	2,5-dihydroxy benzoate
4.	Cephaprin	sodium 5-methoxy salicylate
5.	Cephanone	sodium 3-methoxy salicylate
6.	(6R-cis)-3-[[(Aminocarbonyl oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl)) amino]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin);	sodium salicylate
7.	Carbenicillin	2,5-dihydroxy benzoate
8.	Penicillin G	sodium homovanillate
9.	Ticaricillin	sodium salicylate
10.	Cefazolin	sodium 5-methoxy salicylate
11.	Cepheperin	sodium salicylate
12.	Cephaloridine	sodium salicylate
13.	Cephalosporic C	sodium homovanillate
14.	Cephmetazole	sodium 5-methoxy salicylate
15.	Oxacephalosporin	sodium 3-methoxy salicylate
16.	Penicillin V	sodium salicylate
17.	N—formimidoyl thienamycin monohydrate	2,5-dihydroxy benzoate
18.	Cefuroxine	sodium homovanillate
19.	Carbenicillin	sodium homovanillate
20.	Cefazolin	sodium salicylate
21.	Amoxicillin	sodium 5-methoxy salicylate
22.	Ampicillin	sodium salicylate
23.	Carbenicillin	sodium salicylate
24.	Cephaprin	sodium homovanillate
25.	Oxacephalosporin	2,5-dihydroxy benzoate
26.	Ticaricillin	sodium 5-methoxy salicylate
27.	Carbenicillin	sodium 3-methoxy salicylate
28.	Penicillin V	sodium salicylate
29.	Penicillin G	2,5-dihydroxy benzoate
30.	7-[(hydroxyphenylacetyl)amino]-3-[[(1-methyl-1H—tetrazol-5-yl)-thio]methyul]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cephamandole)	sodium homovanillate
31.	Methacillin	sodium homovanillate
32.	6-[[amino(4-hydroxyphenyl)acetyl]-amino]-3,3-dimethyl--7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid (amoxicillin)	sodium salicylate
33.	Ticaricillin	sodium 5-methoxy salicylate
34.	Cefuroxine	sodium salicylate
35.	Cephamandole	sodium salicylate

As already described, the method of the present invention for enhancing the rate of absorption of drugs from the rectal compartment is useful for a wide range of drugs. Without limiting the broad applicability of the novel method, there is also pointed out below a number of drugs for which the novel method is particularly useful, thus comprising preferred embodiments of the present invention:

(6R-cis)-3-[[Aminocarbonyl)oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin);

N-formimidoyl thienamycin monohydrate

7-[(hydroxyphenylacetyl)amino]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cephamandole)

6-[[amino(4-hydroxyphenyl)acetyl]-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (amoxicillin)

EXAMPLE III

A suppository suitable for human use is preferred using the following ingredients:

	Ingredient	Amount
A.	Sodium 5-methoxy salicylate	500 mg.
B.	Cefoxitin	1 g.
C.	Witepsol ® H-15 suppository excipient[1] [glycerol esters of mixtures of saturated vegetable fatty acids, predominantly lauric acid, derived from purified, specially selected coconut palm kernels, by separation into fatty acid and glyceride portions, fractional distillation of the fatty acid portion, followed by hydrogenation and esterification with glycerin.]	1.5 g.

Dry ingredients A and B are ground together to form a well-mixed, fine powder. Separately, ingredient C is heated to 40°–50° C. till fluid, after which it is mixed with the fine powder mixture of A and B and poured into a mold to form a unit dosage suppository.

In like manner, the following amounts of various drugs may be incorporated into supositories using the same excipient and adjuvant and preparation technique described above:

Drug	Amount
penicillin G	275 mg.
amoxicillin	200 mg.
cephaprin	250 mg.
cephanone	250 mg.
cephalosporin C	275 mg.
ampicillin	500 mg.
carbenicillin	200 mg.
ticaricillin	250 mg.
cefuroxine	250 mg.

-continued

Drug	Amount
cephaloridine	200 mg.
oxacephalosporin	200 mg.
cephaprin	225 mg.
cepheperin	225 mg.
cefazolin	200 mg.
cephamandole	1000 mg.
amoxicillin	500 mg.
N—formimidoyl thienamycin monohydrate	500 mg.

The adjuvants may be chosen from the following salts or their acids.

Sodium 5-methoxysalicylate
Sodium salicylate
Sodium homovanilate
Sodium 2,5-dihydroxybenzoate
Sodium 2,4-dihydroxybenzoate
Sodium 3,4-dihydroxymandelate
Sodium 3-methoxy-4-hydroxymandelate
Sodium 3-methoxy-4-hydroxycinnamate
Sodium 5-methoxy-2-hydroxyphenylsulfonate
Sodium 3-methylsalicylate
Sodium 5-methylsalicylate
Sodium 5-tert-octylsalicylate
Sodium 3-tert-butyl-6-methylsalicylate
Sodium 3,5-diisopropylsalicylate
Sodium 3-tert-butyl-5-methylsalicylate
Sodium quaicolsulfonate
Sodium 5-bromosalicylate
Sodium 3,5-dibromosalicylate
Sodium 5-iodosalicylate
Sodium 3,5-dibromosalicylate
Sodium 2-hydroxyphenylacetate
Sodium 3-hydroxy-2-naphthoate
Sodium mandelate
Sodium phenyllactate
Sodium 2-hydroxyphenylmethanesulfonate
Sodium 5-trifluoromethyl-2-hydroxybenzoate
Sodium 4-hydroxy-3-hydroxyphenylmethanesulfonate
Sodium 3-methoxysalicyalte
Sodium 5-octyloxysalicylate
Sodium 5-butoxysalicylate
Sodium p-hydroxyphenoxyacetate
Sodium 3,4-dihydroxyphenylacetate
Sodium 5-chlorosalicylate
Sodium 3,4-dihdyroxycinnamate
Sodium 3,5-dihydroxybenzoate
Sodium 2-hydroxy-3-methoxybenzoate
Sodium 1-hydroxy-2-naphthoate
Sodium salicylurate

EXAMPLE IV

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of significant drugs which are rectally administered, from the rectal compartment into the blood stream, is demonstrated with an in situ perfusion method of the rectum. The rectum of a male Sprague-Dawley rat weighing 275–300 g., is exposed by an abdominal incision, a glass cannula is inserted in the distal direction and tied firmly to keep it in position. A second cannula is inserted through the anus 1 cm. inside the rectam and secured by ligation. Thus, about 2 cm. of the rectum is exposed to the perfusate. The perfusate (6 ml.) is circulated at a rate of 2 ml./min. at 38° C. As perfusate, 1/15 M-phosphate buffer solutions are used and the ionic strength of the perfusate is adjusted to 0.75 with sodium chloride as necessary. The hydroxyaromatic acid adjuvant is employed at a concentration of 0.5%, while the concentration of the various drugs is varied in accordance with the known effective dosages for said drugs. The amount of drug remaining in the perfusate is analyzed as a function of time by appropriate methods, e.g. by high-pressure liquid chromatography. Blood vessels are also measured by blood samples taken from a vein in the leg of the rat. The results of this method show that the percent absorption of the various drugs after 1 hour from the perfusate in the rat rectum is significantly enhanced by the presence of the adjuvant of the present invention. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

1.	cephalosporin C	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate,
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
2.	amoxicillin	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
3.	ampicillin	Sodium salicylate,
	"	sodium benzoate,
	"	
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
4.	Cefoxitin	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate

-continued

	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
5.	Cefmetazole	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate,
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate

EXAMPLE V

The ability of various of the hydroxyaromatic acid adjuvants of the present invention to enhance the rate of absorption of significant drugs which are rectally administered, from the rectal compartment into the blood stream, is also demonstrated with an in vivo absorption method of the rectum. The rectum of male Sprague-Dawley rat weighing 275–300 g., is exposed by an abdominal incision. A 0.3 ml. sample of the drug solution is injected into a 2 cm. section of the recum and the drug solution is maintained in that section by ligating the rectum with thread. Alternatively, 0.3 ml. of the drug solution is injected into the rectum using a cannula and the anus is tied firmly to prevent leakage of the drug solution. The hydroxyaromatic acid adjuvant is employed at a concentration of 0.5%, while the concentration of the various drugs is varied in accordance with the known effective dosages for said drugs. The amount of drug present in the blood is analyzed as a function of time by extraction with ether at a pH of less than 2.0 after deproteinization with a 3% trichloroacetic acid solution. Following centrifugation, the ether layer is evaporated and the sediment is dissolved in methanol. This methanol sample containing the drug is assayed by high-pressure liquid chromatography. Blood levels are also measured in blood samples taken from a vein in the leg of the rat using a cannula.

The results of this method show that the percent absorption of the various drugs after one hour in the blood stream is significantly enhanced by the presence of the hydroxyaromatic acid adjuvant of the present invention. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

1.	penicillin G	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate,
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate

-continued

	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
2.	carbenicillin	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
3.	methacillin	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate,
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate
4.	Cefmetazole	Sodium salicylate,
	"	sodium benzoate,
	"	sodium o-anisate,
	"	sodium p-anisate,
	"	sodium 3-methoxy
	"	salicylate,
	"	sodium 2,4-dihydroxy
	"	benzoate
	"	sodium 2,5-dihydroxy
	"	benzoate,
	"	sodium 3,5-dihydroxy
	"	benzoate
	"	sodium 2,4-dimethoxy
	"	benzoate
	"	sodium homovanillate
	"	sodium 5-methoxy
	"	salicylate

EXAMPLE VI

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of insulin which is rectally administered, from the rectal compartment into the blood stream, is demonstrated with a microenema technique. Insulin is administered to a male Sprague-Dawley rat weighing 275°–300 g. using a microenema. The microenema is prepared with 0.2 M phosphate buffer, pH 5.0. A volume of 0.3 ml. is delivered rectally. Blood samples are taken from a jugular vein of the rat at designated time intervals. The 0.3 ml. microenema consists of 5 mg. of adjuvant and 1.8 I.U. of insulin. Plasma levels of glucose are measured using the ortho-toluidine method. The results of this method show that plasma glucose levels decrease rapidly after administration of the insulin microenema in the presence of adjuvant. The plasma glucose levels gradually recover from 60 to 120 minutes after administration. The adjuvant greatly enhanced the rectal absorption of

insulin. The following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

Drug	Adjuvant
cephaprin	Sodium salicylate,
"	sodium 5-methoxy
"	salicylate,
"	sodium 3-methoxy
"	salicylate,
"	sodium homovanillate

EXAMPLE VII

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of heparin which is rectally administered, from the rectal compartment into the blood stream, is demonstrated using a microenema technique. A male Sprague-Dawley rat receives 1000 units of heparin (Na salt) dissolved in a 0.1 ml aqueous microenema also containing 20 mg. of absorption adjuvant. The results of this method show that there is a dramatic increase in clotting time after rectal administration of heparin with adjuvant. Clotting times were greater than 90 minutes in blood samples taken at 15 minutes through 90 minutes. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

Drug	Adjuvant
cefazolin	Sodium salicylate,
"	sodium 5-methoxy
"	salicylate,
"	sodium 3-methoxy
"	salicylate,
"	sodium homovanillate

EXAMPLE VIII

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of cefmetazole which is rectally administered, from the rectal compartment into the blood stream, is demonstrated using suppository and microenema formulations. Four male beagle dogs weighing 9.5–11 kg. are used and are fasted for two days prior to experimentation. Witepsol H-15 is used as an excipient to prepare the suppository formulation of cefmetazole. Microenema formulations are prepared with aqueous 0.02 M phosphate buffer with a final pH of 7.4. Either a 1 g. suppository or a 1 ml. microenema is given to each dog. The formulations may contain varying amounts of adjuvant. Blood samples are taken from the foreleg vein at predetermined sampling times after dosing. Blood samples are heparinized and centrifuged at 3,000 rpm for 10 minutes. The concentration of cefmetazole in the plasma of the dogs is analyzed as a function of time using plasma aliquots for the assay of cefmetazole. The results of this method show that the inclusion of adjuvant significantly enhanced the rectal absorption of cefmetazole from both microenema and suppository formulations. The suppository formulations provide greater bioavailabilty of cefmetazole than the microenema formulations as compared with intravenous administration. Following is a table of drugs and adjuvant combinations which are evaluated in accordance with the method described above:

Drug	Adjuvant
Sodium Cefmetazole	Sodium salicylate,
"	sodium 5-methoxy
"	salicylate,
"	sodium homovanillate

EXAMPLE IX

The ability of various of the adjuvants of the present invention to enhance the lymphatic transport of water soluble drugs after rectal administration in conjunction with salicylate-based absorption adjuvants is demonstrated with a microenema technique. A male Sprague-Dawley rat weighing 200–225 g. is anesthetized with pentobarbital and the thoracic duct is cannulated. Flow through this duct includes the mesenteric drainage. Drugs and absorption adjuvants are delivered in the form of a 0.2 ml. aqueous microenema 1/15 M phosphate buffer, at a pH 7.4 (for insulin a pH 5.0). Blood samples (0.3 ml) are taken from the external jugular vein of the rat and centrifuged at 2000 rpm for ten minutes to collect plasma. With the exception of phenol red, determination of drug concentration in plasma and lymph is carried out using a high-pressure liquid chromatography technique at 254 nm. Plasma and lymph samples are deproteinized with acetonitrile. Phenol red is determined at 540 nm after adding 1.0 N sodium hydroxide to the plasma or lymphatic samples. Insulin is assayed with an immunospecific enzyme assay kit supplied by Toyo Jozo Ltd., Japan. The results of this method show that the absorption of the drug in plasma and in lymph collected from the thoracic duct is significantly enhanced by the presence of the hydroxyaromatic acid adjuvant of the present invention. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

	Drug	Adjuvant
1.	(6R—cis)-3-[[(Aminocarbonyl) oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl) amino]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin);	Sodium 5-methoxy salicylate, sodium salicylate
2.	cephalosporin C	Sodium 5-methoxy salicylate, sodium salicylate
3.	penicillin G	Sodium 5-methoxy salicylate, sodium salicylate
4.	methacillin	Sodium 5-methoxy salicylate, sodium salicylate

EXAMPLE X

The ability of various of the dipeptide and metabolites of epinephrine adjuvants of the present invention to enhance the rate of absprption of significant drugs which are rectally admininstered, from the rectal compartment into the blood stream, is demonstrated with a microenema technique. A male Sprague-Dawley rat weighing 225–250 g. is kept fasting for 16 hours prior to the experiment which is conducted under pentabarbitol anesthesia. During the experiment, the rat is kept on a 38° C. surface. The drug with adjuvant is administered rectally as a 0.3 ml microenema using a 0.01 M phosphate buffer at a pH of 7.4 when the depeptide is used as

an adjuvant and at a pH of 4.5 when the metabolites of epinephrine are used. Following administration of the drug solution, the rat anus is ligated with thread to avoid leakage of the solution. Blood samples are taken from the jugular vein at regular intervals and centrifuged at 3000 rpm for 10 minutes to provide a plasma sample. The amount of drug absorbed is analyzed as a function of time by appropriate methods., e.g. by high-pressure liquid chromatography. The results of this method show that plasma levels for the various drugs increased significantly after rectal administration in the presence of an adjuvant and relatively high levels were maintained for over 1.5 hours. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

	Drug	Adjuvant
1.	(6R-cis)-3-[[(Aminocarbonyl) oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl) amino]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin);	Phenylalanyl-phenyl-alanine, 4-hydroxy-3-methoxymandelic acid, 3,4-dihydroxy-mandelic acid
2.	Cefmetazole	phenylalanyl-phenyl-alanine, 4-hydroxy-3-methoxy-mandelic acid 3,4-dihydroxy-mandelic acid
3.	ampicillin	phenylalanyl-phenyl-alanine, 4-hydroxy-3-methoxy-mandelic acid, 3,4-dihydroxy-mandelic acid

EXAMPLE XI

The ability of various of the adjuvants of the present invention to enhance the rate of absorption of significant drugs which are rectally administered, from the rectal compartment into the blood stream, is demonstrated using suppository and microenema formulations. Twelve male beagle dogs weighing 9.5–11 kg. are used and are fasted for 36 hours prior to the experiment. The dogs are divided into three groups of four and crossed over with respect to dosage form. Witepsol H-15 is used as an excipient to prepare with 8% gelatin in saline. Suppositories are administered in the amount of 0.5 g. Mocroenemas are administered with a volume of 0.5 ml. The formulations may contain varying amounts of adjuvant. Blood samples are taken at intervals from the external jugular vein. Blood samples are heparinized and centrifuged at 4000×G for 10 minutes. The plasma levels of the drugs are analyzed as a function of time using plasma aliquots for the assay of drug concentration. The results of this method show that the inclusion of adjuvant significantly enhanced the bioavailability of the drugs in the blood stream. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

	Drug	Adjuvant
1.	$C_{16}H_{17}KN_2O_4S$ (penicillin G)	Sodium 5-methoxy salicylate, sodium salicylate
2.	amoxicillin	sodium 5-methoxy salicylate, sodium salicylate
3.	(6R—cis)-3-[[Aminocarbonyl)	sodium 5-methoxy

-continued

	Drug	Adjuvant
	oxy]methyl]-7-methoxy-8-amino]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin)	salicylate, sodium salicylate

EXAMPLE XII

The ability of various of the hydroxyaromatic acid adjuvants of the present invention to enhance the rate of absorption of insulin which is rectally administered from the rectal compartment into the blood stream, is demonstrated using a microenema technique. A male beagle dog weighing 9.5 t 11 kg. is used. Rectal administration of insulin is in the form of a 0.5 ml. or a 0.25 ml. microenema. Insulin microenema formulation are made up in either 0.9% sodium chloride or in 0.9% sodium chloride with 4% gelatin. Blood samples are taken at intervals for the external jugular vein and treated with EDTA. Blood samples are centrifuged at 4000×G for 10 minutes. Plasma glucose levels are determined at 650 nm using the O-toluidine method. Plasma insulin levels are determined using an immunospecific enzyme assay (Toyo Jozo Company, Ltd., Japan). The results of this method show that the presence of the adjuvant caused a significant decrease in plasma glucose levels concommitant with a large increase in plasma insulin levels. Following is a table of drug and adjuvant combinations which are evaluated in accordance with the method described above:

	Drug	Adjuvant
1.	cepheperin	Sodium 5-methoxy salicylate, sodium salicylate

As already described, the methods of the present invention for enhancing the rate of absorption of drugs from the rectal compartment are useful for a wide range of drugs. Without limiting the broad applicability of the novel methods, there are also pointed out a number of drugs for which the novel methods are particularly useful, thus comprising preferred embodiments of the present invention:

Cephanone
Cephaloridine
Ticaricillin
Cefmetazole;
Carbenicillin
Cefuroxine
(6R-cis)-3-[[(Aminocarbonyl)oxy]methyl]-7-methoxy]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (cefoxitin);
Cephaprin
$C_{16}H_{17}KN_2O_4S$ (penicillin G);
Cefazolin

EXAMPLE XIII

Preparation of Sodium 2-hydroxy-5-methoxy benzenesulfonate

p-Methoxyphenol (12.4 g) was dissolved in chloroform (100 ml) and cooled in ice. Chlorosulfonic acid (11.6 g) was added dropwise to the stirred reaction mixture. The cooling bath was removed after the addition and stirring continued for 24 hours at room temper-

ature. The chloroform was then evaporated off and the residue was vacuum dried to a hygroscopic light brown solid weighing 20.5 g which was 2-hydroxy-5-methoxybenzenesulfonic acid.

NMR ($CDCl_3$) and 3.73 (3H, s, $OC\underline{H}_3$), 6.8-7.2 (3H, m, aromatic $\underline{H}$), and 9.86 (2H, broad s, $O\underline{H}$ and $SO_3\underline{H}$). IR (film) 3500–2900, 1512, 1470, 1229, 1198, 996, 938 cm^{-1}.

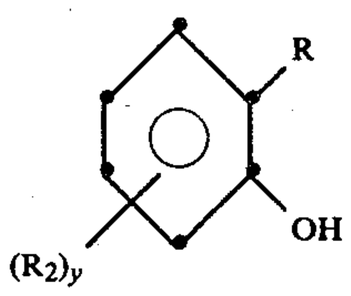
The above sulfonic acid (10 g) was dissolved in water (10 ml) and poured into 75 ml of saturated sodium chloride solution. A white solid separated immediately. It was filtered and dried. Crystallization from water gave the pure sodium salt of 2-hydroxy-5-methoxybenzenesulfonic acid (6.6 g).

NMR (D_2O) and 3.83 (3H, s, $OC\underline{H}_3$), 7.05 and 7.33 (3H, multiplets, aromatic). IR (KBr) 3260, 1518, 1440, 1300, 1280, 1240, 1210, 1905, 1045 cm^{-1}.

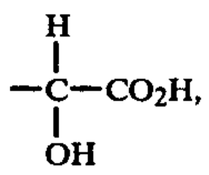
While in the foregoing there has been provided a detailed description of particular embodiments of the present invention, it is to be understood that all equivalents obvious to those having skill in the art are to be included within the scope of the invention as claimed.

What we claim and desire to secure by Letters Patent is:

1. A method for enhancing the rate of absorption of a rectally administered β-lactam antibiotic drug from a rectal compartment into the blood stream, said method comprising the steps of preparing a β-lactam drug form capable of being rectally administered, said drug form comprising a therapeutically effective dosage amount of a drug selected from the group consisting of a thienamycin, penicillin or cephalosporin capable of being absorbed into the blood stream from the rectal compartment and an adjuvant of the formula:



wherein R_1 is CO_2H, $(CH_2)COOH$,



SO_3H, or a pharmaceutically acceptable salt thereof wherein R_2 is OH, H, a lower alkoxy radical, a lower alkyl radical, a halo radical, or a tri-halo lower alkyl radical, and wherein y is an integer of 1 or 2, said adjuvant being present in said drug form in a sufficient amount to be effective in enhancing said absorption rate, and administering said drug form into said rectal compartment.

2. The method of claim **1** wherein said drug is selected from the group consisting of penicillin G., ampicillin, amoxicillin, methacillin, carbenicillin, cefoxitin, cephamandole, cephmetazole, cephanone, oxacephalosporin, or N-formimidoyl thienamycin.

3. The method of claim **1** wherein said drug comprises cefoxitin.

4. The method of claim **1** wherein said adjuvant is 5-methoxysalicylic acid, salicylic acid, homovanillic acid; 2,5-dihydroxybenzoic acid; 2,4-dihydroxybenzoic acid; 5-methoxy-2-hydroxyphenylsulfonic acid; 3-methylsalicylic acid; 5-methylsalicylic acid; 5-tert-octylsalicylic acid; 3-tert-butyl-6-methylsalicylic acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-5-methylsalicylic acid; guaicolsulfonic acid; 5-bromosalicylic acid; 3,5-dibroamosalicylic acid; 5-iodosalicylic acid; 3,5-diiodosalicylic acid; 3,5-diiodosalicylic aci; 2-hydroxyphenylacetic acid; 2-hydroxyphenylmethanesulfonic acid; 5-trifluoromethyl-2-hydroxybenzoic acid; 3-methoxysalicylic acid; 5-octyloxysalicylic acid; 5-butoxysalicylic acid; 5-chlorosalicylic acid; 2-hydroxy-3-methoxy-benzoic acid; or the sodium salts thereof.

5. The method of claim **1** wherein said adjuvant is 5-methoxysalicylic acid, or homovanillic acid and the sodium salts thereof.

6. The method of claim **1** wherein the adjuvant is salicylic acid or sodium salicylate.

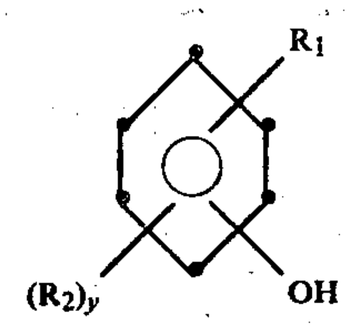
7. The method of claim **1** wherein said administering step is carried out at a pH of below 5.5 or above 7.5.

8. The method of claim **1** wherein said drug form is a suppository.

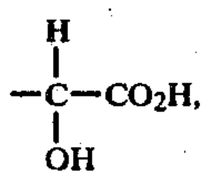
9. The method of claim **1** wherein said suppository comprises a soft elastic gelatin capsule containing said drug and said adjuvant.

10. The method of claim **1** wherein said administering step is accomplished by a microenema.

11. A rectally administered drug form comprising a therapeutically effective dosage amount of a drug selected from the group consisting of a thienamycin, penicillin or cephalosporin capable of being absorbed into the blood stream from a rectal compartment and an adjuvant



wherein R_1 is CO_2H, $(CH_2)COOH$,



SO_3H, or a pharmaceutically acceptable salt thereof wherein R_2 is OH, H, a lower alkoxy radical, a lower alkyl radical, a halo radical, or a tri-halo lower alkyl radical, and wherein y is an integer of 1 or 2, said adjuvant being present in said drug form in a sufficient amount to be effective in enhancing the absorption rate of said drug from from said rectal compartment into the bloodstream.

12. The drug form of claim **11** wherein said drug is selected from the group consisting of penicillin G., ampicillin, amoxicillin, methacillin, carbenicillin, cefoxitin, cephamandole cephaprin, cephmetazole, cephanone, oxacephalosporin, or N-formidoyl thienamycin.

13. The drug form of claim **11** wherein said drug comprises cefoxitin.

14. The drug form of claim **11** wherein said adjuvant is 5-methoxysalicylic acid, salicylic acid, homovanillic acid; 2,5-dihydroxybenzoic acid; 2,4-dihydroxybenzoic acid; 5-methoxy-2-hydroxyphenylsulfonic acid; 3-methylsalicylic acid; 5-methylsalicylic acid; 5-tert-

octylsalicylic acid; 3-tert-butyl-6-methylsalicylic acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-5-methylsalicylic acid; guaicolsulfonic acid; 5-bromosalicylic acid; 3,5-dibroamosalicylic acid; 5-iodosalicylic acid; 3,5-diiodosalicylic acid; 3,5-diiodosalicylic acid; 2-hydroxyphenylacetic acid; 2-hydroxyphenylmethanesulfonic acid; 5-trifluoro-methyl-2-hydroxybenzoic acid; 3-methoxy-salicylic acid; 5-octyloxysalicylic acid; 5-butoxy-salicylic acid; 3,4-dihydroxyphenylacetic acid; 5-chlorosalicylic acid; 2-hydroxy-3-methoxybenzoic acid; salicyluric acid; or the sodium salts thereof.

15. The drug form of claim **11** wherein said adjuvant is 5-methoxysalicylic acid, or homovanillic acid, and the sodium salts thereof.

16. The drug form of claim **11** wherein the adjuvant is salicylic acid or sodium salicylate.

17. The drug form of claim **11** wherein said administering step is carried out at a pH of below 5.5 or above 7.5.

18. The drug form of claim **11** wherein said drug form is a suppository.

19. The drug form of claim **18** wherein said suppository comprises a soft elastic gelatin capsule containing said drug and said adjuvant.

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